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Research article

Spectrum and genotype–phenotype relationship of *ALPK3* variants in Chinese patients with hypertrophic cardiomyopathy

Jing Wang [a,b,1], Fang Wang [c,1], Guixin Wu [d,e], Minjie Lu [d], Channa Zhang [d], Lei Song [d,e,f], Yibing Shao [b], Jizheng Wang [d,**], Fusong Liu [c,***], Mei Zhang [a,*]

[a] *Department of Cardiology, Qilu Hospital of Shandong University, Jinan, 250012, Shandong, China*
[b] *Department of Cardiology, Qingdao Municipal Hospital, Qingdao, 266071, Shandong, China*
[c] *Department of Cardiology, The Third People's Hospital of Qingdao City, Qingdao, 266041, Shandong, China*
[d] *State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100037, China*
[e] *Cardiomyopathy Ward, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100037, China*
[f] *National Clinical Research Center for Cardiovascular Diseases, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100037, China*

A R T I C L E I N F O

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ALPK3
Truncating variant
Missense variant

A B S T R A C T

Background: Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disease, and it has obvious genetic and clinical heterogeneity. Recently, heterozygous *ALPK3* truncating variants (*ALPK3*tv) have been shown to cause HCM. However, the spectrum of *ALPK3* variants and their relationships with the clinical characteristics of Chinese patients with HCM remain to be elucidated.

Methods and results: Whole-exome sequencing data from 986 patients with HCM and 761 controls without HCM were utilized to analyze *ALPK3* variants. Eleven *ALPK3*tv were detected in 18 patients with HCM (1.8 %), while no such variants were identified in controls. We also detected 21 rare *ALPK3* missense variants in 16 patients with HCM (1.6 %) and 8 controls (1.1 %), respectively. *ALPK3*tv were significantly enriched in patients with HCM ($P < 0.001$), whereas the prevalence of missense variants was comparable between the HCM and control groups ($P = 0.309$). Patients with *ALPK3*tv exhibited a significantly lower left ventricular outflow tract gradient ($P = 0.011$) and a higher prevalence of apical HCM (27.8 %; $P = 0.008$).

Conclusions: Our study supports that heterozygous *ALPK3*tv, but not *APLK3* missense variants, are a genetic cause of HCM. Patients with HCM carrying *ALPK3*tv have a greater likelihood of developing apical HCM.

* Corresponding author.
** Corresponding author.
*** Corresponding author.
E-mail addresses: jzwang@hotmail.com (J. Wang), lfs118@126.com (F. Liu), daixh@vip.sina.com (M. Zhang).
[1] These authors contributed equally to this work.

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1. Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disease with an estimated prevalence of approximately 1 in 200–500 individuals in the general population [1]. HCM is characterized by substantial clinical heterogeneity, with a diverse natural history and morphology, as well as heterogeneous clinical manifestations and outcomes. Although HCM is the leading cause of sudden cardiac death (SCD) in young people and an important cause of heart transplantation, most patients with HCM will not suffer from these catastrophic complications during their lifetime. The genetic etiology of HCM is also largely heterogeneous. To date, more than 20 genes have been reported to be related to HCM, and causal genetic defects can be identified in approximately half of patients with HCM. Variants in the genes encoding sarcomere proteins account for most cases of genetic-positive HCM, and the causality of these genes is definitive [2]. However, the contribution of additional genes, such as those encoding Z-disc proteins, is not well known, and their association with HCM lacks robust supporting evidence [3].

Recently, *ALPK3* has been proposed as an HCM-causing gene [4–6]. *ALPK3* is located at 15q25.2, contains 14 exons, and is highly expressed in the heart throughout all stages of life. Recent studies have revealed that *ALPK3* is a pseudokinase that is prominently expressed at the sarcomere M-band and the nuclear envelope of cardiomyocytes. *ALPK3* plays an indispensable role in regulating the force-buffering capacity of cardiomyocytes and in regulating the expression of M-band proteins, both in vitro and in vivo [4,7]. The potential impact of *ALPK3* variants on the expression of the encoded protein, alpha-protein kinase 3, as well as its interaction with binding partners or subcellular localization, may lead to impaired cardiomyocyte structure and function.

Homozygous *ALPK3* truncating mutations (*ALPK3*tv) have been reported to cause severe pediatric cardiomyopathy and extracardiac manifestations, such as contractures, scoliosis, cleft palate, and facial dysmorphisms in humans [8,9]. Consistently, *Alpk3*--knockout mice exhibit cardiomyopathy with left ventricular (LV) dilatation and hypertrophy [10]. Moreover, recent studies have suggested that heterozygous *ALPK3*tv can cause adult HCM in an autosomal-dominant manner [5,11,12]. However, the genetic and clinical spectra of *ALPK3* variants in Chinese patients with HCM are still unclear.

In this study, we analyzed *ALPK3* variants in a large cohort of Chinese patients with HCM and investigated the correlation between *ALPK3* variants and the clinical manifestations of HCM.

2. Methods

2.1. Participants

A total of 1039 Chinese patients with HCM were consecutively enrolled between 2012 and 2018 at Fuwai Hospital, Chinese Academy of Medical Sciences, Beijing, China. The diagnostic criteria for HCM were the presence of a maximal end-diastolic LV wall thickness of $\geq$15 mm, or $\geq$13 mm if there was a familial history of HCM, on echocardiography or cardiac magnetic resonance imaging in the absence of other metabolic or systemic diseases sufficient to cause the observed abnormality, such as severe hypertension or valvular disease. Baseline data, including demographic information, medical history, and echocardiography and cardiac magnetic resonance imaging results, were gathered at the time of patient enrollment. Additionally, 823 sex-, age-, and ethnicity matched individuals without HCM were recruited during the same timeframe at Fuwai Hospital as control participants. The presence of HCM was excluded in all control participants by echocardiography.

The study protocol complied with the principles of the Declaration of Helsinki and was approved by the ethics committees of Fuwai Hospital. Written informed consent was obtained from all participants.

2.2. Genotyping and variant filtering

Whole-exome sequencing was performed on genomic DNA isolated from peripheral blood mononuclear cells. The Agilent SureSelectXT Human All Exon V6 kit was used to construct sequencing libraries and capture exomic regions. Paired-end sequencing of 2 $\times$ 150 bp was performed on the Illumina NovaSeq platform according to the manufacturer's protocol, and the obtained reads were aligned to Genome Human Build 37 (GRCh37/hg19).

Variants were called using the Genome Analysis Toolkit v3.8 [13] and annotated to canonical transcripts using SnpEff [14]. A total of 25 patients with HCM and 12 controls were excluded owing to excessive missing rates or excessive heterozygosity, both defined as being 1.5-times the interquartile range above the third quartile. Additionally, 14 patients with HCM and 50 controls were excluded because their mean identical-by-descent sharing with other individuals was $>$0.125. This estimation was made after linkage disequilibrium pruning using PLINK [15]. Fourteen patients were excluded because they had mutations in *GLA*, *LAMP2*, or *PRKAG2*, as described previously [16].

Variants in *ALPK3* were described in accordance with Human Genome Variation Society recommendations and annotated on the basis of the longest transcript of *ALPK3* (NM_020778.4) [17]. Rare variants were defined as those with a minor allele frequency of $<$0.01 in the discovery cohort. The variants with a minor allele frequency of $>$0.0001 in all genomeAD sub-populations were excluded (https://gnomad.broadinstitute.org/). Truncating variants were defined as variants that altered the full-length protein encoded by *ALPK3*, including nonsense, frameshift, and splice-site mutations affecting positions $\pm$1 and $\pm$ 2. Missense variants with a Combined Annotation-Dependent Depletion (CADD) score of $\leq$15 or a Genomic Evolutionary Rate Profiling score (GERP) of $\leq$2 were excluded [18,19]. All *ALPK3* candidate variants were verified by Sanger sequencing.

Variants in eight sarcomere genes (*MYH7*, *MYBPC3*, *TNNT2*, *TNNI3*, *MYL2*, *MYL3*, *TPM1*, and *ACTC1*) were classified using the criteria of the American College of Medical Genetics and Genomics [20]. Patients were divided into sarcomere-positive (SARC+) and sarcomere-negative (SARC−) groups depending on whether they carried any pathogenic variants or likely pathogenic variants in sarcomere genes.

2.3. Follow-up and endpoints

Follow-up was conducted annually via clinic visit or telephone interview until March 2022. The primary endpoint was cardiovascular death owing to cardiogenic or vascular causes, encompassing SCD, heart failure (HF)-related death, and stroke-related death. SCD was defined as unexpected death due to cardiac causes that occurred within 1 h of symptom onset in a person with known or unknown cardiac disease, or nocturnal death with no antecedent history of worsening symptoms. Appropriate implantable cardioverter-defibrillator intervention and rescue from cardiac arrest were considered equivalent to SCD. HF-related death was defined as death preceded by symptoms of HF for >1 h or heart transplantation at end-stage HF. The follow-up time was defined as the duration from enrollment to the endpoint or final follow-up.

2.4. Statistical analysis

The data were analyzed using GraphPad Prism (version 9.0) and SPSS Statistics (IBM Corporation, version 26.0). Continuous variables are presented as the mean ± standard deviation and categorical variables as n (%). We used the independent-samples *t*-test or one-way analysis of variance followed by the least significance difference test or Games-Howell post hoc analysis, as appropriate, to compare continuous data. To compare categorical data, the chi-square test or Fisher's exact test was used, as appropriate. Survival curves were generated using the Kaplan–Meier method and were compared using the log-rank test to assess event-free survival differences among the groups. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Study participants

Overall, 986 patients with HCM and 761 controls without HCM were included in the final analysis. The baseline characteristics of the participants are shown in Supplementary Table S1. The mean age of the patients in the HCM group was 47.8 ± 14.4 years at enrollment; 639 patients (64.8 %) were male; and 323 patients (32.8 %) had pathogenic variants or likely pathogenic variants in eight sarcomeric genes associated with HCM (*MYH7*, *MYBPC3*, *TNNT2*, *TNNI3*, *MYL2*, *MYL3*, *TPM1*, and *ACTC1*). There was no significant difference in sex or age at enrollment between the HCM group and the control group.

3.2. Variant profile of ALPK3 in Chinese patients with HCM

A total of 63 rare non-synonymous variants in the *ALPK3* gene were identified, including 11 truncating and 52 missense variants. Among them, 31 missense variants were rejected because of a CADD score of ≤15 or a GERP score of ≤2. Finally, 32 rare *ALPK3* variants were included for subsequent analysis, which consisted of 21 missense and 11 truncating variants (8 frameshift deletions and 3 nonsense mutations) (Supplementary Table 2). No splicing variants were detected.

Among the identified *ALPK3* missense variants, 14 were detected in 16 patients (1.6 %), and 7 were detected in 8 controls (1.1 %). One patient with HCM harbored two rare *ALPK3* variants, and no variants were detected in both the HCM and control groups. The frequency of rare *ALPK3* missense variants was comparable between the HCM group and the control group (odds ratio 1.553, 95 % confidence interval 0.661–3.647, $P = 0.309$). Specifically, these *ALPK3* missense variants were identified in 6 (1.9 %) and 10 (1.5 %) SARC+ and SARC− patients, respectively, with a similar prevalence in these two groups ($P = 0.684$).

Notably, all 11 *ALPK3*tv were identified only in patients with HCM ($n = 18$ [1.8 %]); none were found in control participants. Six patients carried nonsense variants, and 12 patients harbored *ALPK3* frameshift variants. Compared with the control group, *ALPK3*tv were significantly enriched in the HCM group ($P < 0.001$). Moreover, *ALPK3*tv were more frequently detected in SARC− patients than in SARC + patients (16/663[2.4 %] and 2/323 [0.6 %] patients, respectively; $P = 0.048$).

3.3. Clinical characteristics of patients with HCM with ALPK3 variants

The clinical characteristics of patients with *ALPK3* missense variants are summarized in Table 1. Carriers of *ALPK3* rare missense variants presented comparable clinical expressions to both the SARC+ and SARC− groups (Table 1).

Patients with *ALPK3*tv had a significantly lower left ventricular outflow tract (LVOT) gradient than SARC+ ($P = 0.002$) and SARC− ($P = 0.001$) patients (Table 2). Consistently, 182 of 321 (57.8 %) SARC + patients and 350 of 647 (55.0 %) SARC− patients had LVOT

Table 1
Demographic and clinical characteristics of patients with HCM with and without *ALPK3* missense variants.

	Carriers with missense variants of *ALPK3* (n = 16)	SARC+ (n = 317)	SARC− (n = 653)	*P*-value[a]	*P*-value[a]	
					ALPK3 vs. SARC+	*ALPK3* vs. SARC-
Male, n (%)	12 (75.0 %)	203 (64.0 %)	422 (64.6 %)	0.670	0.371	0.390
Age at diagnosis, yrs	40.94 ± 13.96	38.96 ± 14.24	45.71 ± 14.22	**<0.001**	0.588	0.185
Age at enrollment, yrs	44.31 ± 14.17	43.85 ± 14.66	50.13 ± 14.01	**<0.001**	0.899	0.106
LVEDD, mm	43.31 ± 6.64	42.56 ± 6.19	44.66 ± 6.42	**<0.001**	0.644	0.400
Left atrium, mm	39.63 ± 8.12	42.97 ± 7.83	41.31 ± 6.75	**0.002**	0.269	0.694
Maximal LVWT, mm	24.63 ± 4.94	24.11 ± 5.84	21.82 ± 5.77	**<0.001**	0.729	0.056
Apical hypertrophy，n (%)	3 (18.8 %)	19 (6.1 %)	56 (8.7 %)	0.088	0.083	0.164
LVEF, %	68.47 ± 8.26	67.84 ± 7.95	67.39 ± 8.27	0.652	0.764	0.601
LVOT obstruction, n (%)	8 (53.3 %)	178 (57.2 %)	349 (54.3 %)	0.683	0.766	0.942
LVOT gradient，mmHg	30.99 ± 27.86	46.46 ± 37.53	49.05 ± 45.39	0.207	0.172	0.107
FMH,n (%)	3 (18.8 %)	104 (32.8 %)	91 (13.9 %)	**<0.001**	0.240	0.481

Continuous variables are presented as the mean ± standard deviation, and categorical variables are presented as number (n) and percentage (%). SARC+, sarcomere-positive; SARC−, sarcomere-negative; LVEDD, left ventricular end-diastolic diameter; LVWT, left ventricular wall thickness; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; FMH, family medical history.

[a] Continuous variables were compared using one-way analysis of variance, and categorical variables were compared using chi-square test or Fisher's exact test, as appropriate. Bold indicates $P < 0.05$.

obstruction, whereas only 3 of 18 patients (16.7 %) with *ALPK3*tv had LVOT obstruction ($P = 0.003$). Moreover, 5 of 18 patients (27.8 %) with *ALPK3*tv presented apical HCM, which is significantly higher than the proportion of SARC+ and SARC− patients who presented apical HCM ($P = 0.008$).

3.4. Follow-up and outcomes of ALPK3 heterozygotes

A total of 43 patients were lost to follow-up, including 2 patients with *ALPK3*tv. During the follow-up period of 5.31 ± 2.10 years (5007patient-years), 57 patients suffered cardiovascular death, including 31 patients with SCD, 11 with HF-related death, and 5 with stroke-related death. One patient (1/16, 6.3 %) with *ALPK3* missense variants died of SCD. One *ALPK3*tv carrier (1/16, 6.3 %) died of SCD. Patients with *ALPK3*tv and *ALPK3* missense variants did not have a higher risk of cardiovascular death than SARC+ (6.2 %, 19/306) and SARC− patients (6.0 %, 36/605; $P = 0.983$). The survival analysis showed a similar incidence of freedom from cardiovascular death between *ALPK3*tv, SARC+, and SARC− patients ($P = 0.978$, Fig. 1). .

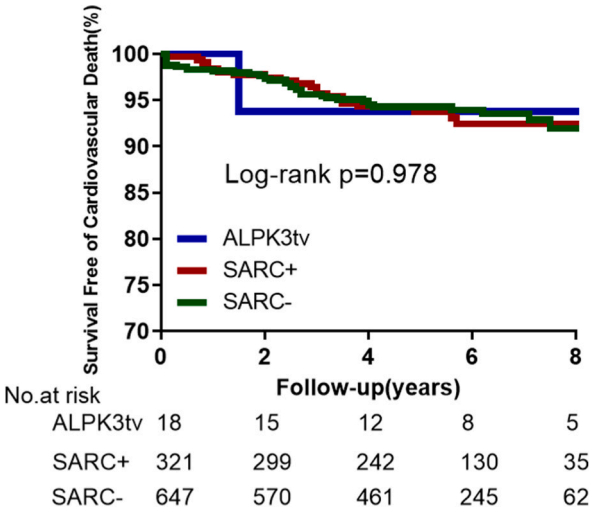

Fig. 1. Kaplan-Meier analysis comparing freedom from cardiovascular death between *ALPK3*tv, SARC+, and SARC− patients. Patients with HCM with *ALPK3*tv did not have a higher risk of cardiovascular death than the other patients. *P*-values were calculated using the log-rank test.

Table 2
Demographic and clinical characteristics of patients with HCM with and without *ALPK3*tv.

	Carriers with *ALPK3*tv (n = 18)	SARC+ (n = 321)	SARC- (n = 647)	*P*-value[a]	*P*-value	
					ALPK3 vs. SARC+	*ALPK3* vs. SARC-
Male, n (%)	14 (77.8 %)	206 (64.2 %)	417 (64.5 %)	0.497	0.239	0.243
Age at diagnose, yrs	40.83 ± 16.05	39.07 ± 14.14	45.72 ± 14.23	**<0.001**	0.609	0.151
Age at enrollment, yrs	44.67 ± 15.56	43.99 ± 14.54	50.11 ± 14.04	**<0.001**	0.845	0.110
LVEDD, mm	43.67 ± 5.61	42.59 ± 6.13	44.66 ± 6.49	**<0.001**	0.486	0.515
Left atrium, mm	38.61 ± 6.53	42.98 ± 7.81	41.33 ± 6.78	**0.001**	**0.033**	0.217
Maximal LVWT, mm	24.22 ± 7.63	24.07 ± 5.73	21.83 ± 5.75	**<0.001**	0.915	0.084
Apical hypertrophy，n (%)	5 (27.8 %)	19 (6 %)	54 (8.4 %)	**0.008**	**0.006**	**0.017**
LVEF, %	67.17 ± 6.92	67.83 ± 7.87	67.42 ± 8.34	0.752	0.739	0.898
LVOT obstruction, n (%)	3 (16.70 %)	182 (57.8 %)	350 (55 %)	**0.003**	**0.001**	**0.001**
LVOT gradient, mmHg	19.18 ± 28.51	46.71 ± 37.45	49.37 ± 45.33	**0.011**	**0.002**	**0.001**
FMH, n (%)	2 (11.1.%)	106 (33 %)	90 (13.9 %)	**<0.001**	0.052	1.000

Continuous variables are presented as the mean ± standard deviation, and categorical variables are presented as number (n) and percentage (%). SARC+, sarcomere-positive; SARC−, sarcomere-negative; LVEDD, left ventricular end-diastolic diameter; LVWT, left ventricular wall thickness; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; FMH, family medical history.

[a] Continuous variables were compared using one-way analysis of variance, and categorical variables were compared using chi-square test or Fisher's exact test, as appropriate. Bold indicates $P < 0.05$.

4. Discussion

We conducted an analysis of rare *ALPK3* variants in Chinese patients with HCM and individuals without HCM as controls. The involvement of *ALPK3* in cardiomyopathy was initially observed in 2016, when patients with biallelic *ALPK3*tv exhibited early-onset and severe cardiomyopathy, along with extracardiac manifestations, such as facial dysmorphism, scoliosis, and cleft palate [8]. Several case studies have verified that biallelic *ALPK3*tv causes severe cardiomyopathy late in gestation or infancy with biventricular dilatation and depressed contractile function [11,21,22]. Moreover, recent reports have indicated that heterozygous *ALPK3*tv are associated with HCM [5,6]. Our research findings are consistent with these previous studies, and we successfully confirmed the increased prevalence of *ALPK3*tv in the HCM population.

A previous study revealed that the prevalence of heterozygous *ALPK3*tv in an East Asian cohort was 0.6 %, which was significantly lower than the prevalence in a European cohort (1.6 %) [6]. However, in our Chinese cohort, approximately 1.8 % of patients with HCM harbored heterozygous *ALPK3*tv, which is more consistent with the European cohort reported previously, suggesting that the prevalence of heterozygous *ALPK3*tv may actually be similar between Europe and East Asia.

The relevance of *ALPK3* missense variants in relation to HCM remains uncertain. *ALPK3* missense variants are more prevalent in East Asian patients with HCM than in the control subset from the Genome Aggregation Database, suggesting a potential association between *ALPK3* missense variants and HCM [6]. However, our study did not observe a higher occurrence of rare missense variants in *ALPK3* among patients with HCM than in controls. In line with our findings, Herkert et al. evaluated the frequency of *ALPK3* variants in a Dutch cohort of 1548 patients with cardiomyopathy and a US cohort of 149 patients with cardiomyopathy [12]. The frequency of *ALPK3* missense variants was not higher compared with the general population. Further research is necessary to explore the causal role of *ALPK3* missense variants in HCM and their potential influence on the phenotype of patients with HCM.

It is worth noting that *ALPK3*tv were exclusively identified in patients with HCM within our study population, and their presence was more commonly detected in SARC− patients than in SARC + patients. However, the occurrence of *ALPK3* missense variants in both the SARC+ and SARC− groups was comparable. This finding suggests that *ALPK3*tv have a higher level of certainty in their pathogenic nature compared with *ALPK3* missense variants. Consequently, this observation further reinforces the notion that the pathogenic mechanism of *ALPK3* is dependent on loss of function.

The result of this study, as well as previous studies, suggests that the clinical phenotype of patients with heterozygous *ALPK3*tv differs significantly from those with biallelic variants. The notable difference is that patients with heterozygous *ALPK3*tv are diagnosed in adulthood and exhibit minimal extracardiac symptoms. Lopes et al. observed a higher likelihood of apical or concentric HCM in patients with *ALPK3*tv [5]. Similarly, our study demonstrated a lower LVOT gradient and a significantly higher prevalence of apical HCM in patients with *ALPK3*tv than in those without. These findings offer compelling evidence that supports the association between apical HCM and the presence of *ALPK3*tv.

Currently, our understanding of the prognosis of patients with HCM with *ALPK3* variants is limited. Lopes et al. observed that patients with *ALPK3*tv exhibited a significantly higher occurrence of HF-related mortality or need for heart transplantation than SARC− patients. Nevertheless, in the present study, patients with *ALPK3*tv exhibited a similar rate of cardiovascular mortality to SARC- patients. Additionally, we examined the prognosis of patients with *ALPK3* missense variants compared with those without *ALPK3* missense variants. Our findings indicate that patients with *ALPK3* missense variants do not face an increased risk of cardiovascular death. However, it is important to note that our study only observed one cardiovascular death in a patient with *ALPK3*tv and one in a patient with *ALPK3* missense variants. Consequently, the limited number of events may not provide sufficient statistical power to draw definitive conclusions about prognosis. To provide a more comprehensive understanding of prognosis, further research in a larger cohort with an extended follow-up period is necessary.

5. Conclusions

*ALPK3*tv were enriched in patients with HCM and were associated with an increased risk of apical HCM and a low possibility of LVOT obstruction. Further studies are essential to ascertain the pathogenicity of heterozygous *ALPK3* missense variants.

Ethics Approval and consent to participate

The study was reviewed and approved by the Ethics Committees of Fuwai Hospital, with the approval number:2018–989. Written informed consent was obtained from all patients.

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Data availability statement

The data will be published in the future, so we are not making our data public at the moment. The data used in current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Jing Wang: Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Fang Wang:** Writing – review & editing, Investigation, Formal analysis. **Guixin Wu:** Writing – review & editing, Methodology, Formal analysis. **Minjie Lu:** Investigation, Data curation. **Channa Zhang:** Project administration. **Lei Song:** Supervision, Resources, Funding acquisition. **Yibing Shao:** Formal analysis. **Jizheng Wang:** Writing – review & editing, Methodology, Funding acquisition. **Fusong Liu:** Resources, Formal analysis. **Mei Zhang:** Writing – review & editing, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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List of abbreviations

HCM	hypertrophic cardiomyopathy
*ALPK3*tv	*ALPK3* truncating variants
SCD	sudden cardiac death
LV	left ventricular
CADD	Combined Annotation-Dependent Depletion
GERP	Genomic Evolutionary Rate Profiling score
SARC+	sarcomere-positive
SARC−	sarcomere-negative
HF	heart failure
LVEDD	left ventricular end-diastolic diameter
LVWT	left ventricular wall thickness
LVEF	left ventricular ejection fraction
LVOT	left ventricular outflow tract
FMH	family medical history

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e32786.

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